

DOES LEVOSIMENDAN OFFER RENAL PROTECTION DURING OFF PUMPCORONARY ARTERY BYPASS GRAFTING SURGERY? USE OF PLASMA NEUTROPHIL GELATINASE-ASSOCIATED LIPOCALIN(N-GAL) AS AN EARLY MARKER OF AKI

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Introduction:

Acute renal injury (AKI) is a severe complication that occurs in 3.5-31.0% of patients undergoing on/off pump cardiac surgery.¹ Manipulations of heart during off pump Coronary Artery Bypass Grafting (CABG) causes hemodynamic instability which leads to reduction in cardiac output which can cause AKI in postoperative period.² The occurrence of AKI in patients undergoing cardiac surgery raises the mortality rate from 0.4-4.4% to 1.3-22.3% making severe postoperative AKI an independent risk factor for mortality that results in an 8-fold increase in the risk of death.¹ The early identification of patients at risk of developing AKI after cardiac surgery is an important strategy for improving the care of such patients during the intraoperative and postoperative periods.¹

Serum creatinine is not an early or reliable marker for AKI as it takes time to rise. Human neutrophil gelatinase - associated lipocalin (NGAL) was initially identified as a protein isolated from the secondary granules of human neutrophils.³

In 2005, Mori et al. clarified that NGAL accumulates in the human kidney cortical tubules and in the blood and urine after nephrotoxic and ischemic injury.⁴ and Mishra et al. reported that the NGAL concentration in urine and serum represents a sensitive, specific, and highly predictive early biomarker for acute renal injury after cardiac surgery.⁵

Levosimendan acts by increasing the calcium sensitivity of myocardial cells (inotropy) and opening the ATP sensitive K⁺ channels (vasodilation). The action on K⁺ channels in mitochondria seems to have a protective effect on myocardial, renal and other organs from ischemic injury.⁶

We hence hypothesized that in off-pump CABG the renal-protective effect of levosimendan can be predicted by measurement of N-GAL levels.

Patients & methods :

After the approval of institutional ethics committee the current study was done in KEM hospital, Mumbai. A total of 60 Patients of either sex posted for Off Pump CABG were enrolled for the study. Informed and written consent were taken from the study participants. 4 patients were excluded from our study due to emergency conversion to on-pump CABG.

All patients were anesthetized via standard institutional protocol using Inj. Etomidate 0.3 mg/kg; Inj. fentanyl 10mcg/kg; Inj. Rocuronium 1.2mg/kg and were maintained on oxygen + air +

sevoflurane (0.5-1 MAC). Continuous infusion of inj. Midazolam (0.02mg/kg/hr) + inj.fentanyl (2mcg/kg/hr) + inj.Rocuronium (0.2mg/kg/hr) was maintained. All patients were operated by the same surgical team. Alternate eligible patients were allocated to two different groups. After induction patients in **Group L** received a loading dose of inj.levosimendan 6mcg/kg over 10 minutes followed by 0.1mcg/kg/min for 24 hours and another inotrope (noradrenaline @ 0.02-mcg) was added to maintain mean arterial pressure > 65mmHg as and when required. Patients in control **Group C** received standard (dobutamine @ 5mcg/kg/min and noradrenaline @ 0.02-0.2 mcg/kg/min) inotropes during CABG. Heart rate (HR), Arterial Blood Pressure (ABP), pulse oximetry, cardiac index (CI), and pulmonary capillary wedge pressure (PCWP), Central venous pressure (CVP), urine output, capnography, nasal temperature, and arterial blood gases (ABG) were monitored continuously. Hemodynamic parameters were recorded at T₀= baseline parameters, T₁= during anastomoses, T₂= end of surgery, T₃= 6 hrs after surgery in ICU, T₄= 12 hrs after surgery in ICU, T₅ = 24 hrs after surgery in ICU. Levosimendan infusion was stopped after 24 hrs. To obviate postoperative volume depletion and prerenal azotemia, patients received at least 80% of their maintenance requirements during the first 24 hours after surgery and 100% maintenance subsequently.

Preoperative plasma sample for N-GAL as baseline, at 2 hours after surgery and 24 hrs after surgery were collected. Serum Creatinine was measured before Surgery and 24hrs post-op and then every day till discharge from ICU. AKI was defined according to the Acute Kidney Injury Network (AKIN) criteria: an absolute (≥ 0.3 mg/dl) or percentage ($\geq 50\%$) increase in serum creatinine or a reduction in urine output <0.5 ml/kg/h for > 6 h, or the need for renal replacement therapy. Other parameters like cardiac index, dialysis requirement, length of hospital stay and mortality were measured.

As for statistical analysis Student's *t*-test was used for parametric data. Fisher's exact test and chi square test were used to compare categorical data. *P*-value < 0.05 was considered significant.

Results:

In our study 60 patients posted for off-pump CABG were categorized into 2 groups of 30 each and were studied. The mean age of the patients in either group were comparable (59.9 ± 8.84) Vs (61.32 ± 7.64).

No significant difference was observed between the two groups in the baseline N-GAL levels measured pre-operatively (3.52 ± 2.1 in group L Vs 2.76 ± 1.02 group C). Though an increase in N-GAL levels immediately after surgery was observed in both the groups, the rise in group C patients was significantly higher (2.76 ± 1.02 - 7.31 ± 2.03 ng/ml with *p* value 0.03) than patients in Group L (3.52 ± 2.16 to 6.9 ± 4.33 ng/ml with *p* value 0.001) (fig.1). In addition to the above mentioned observation the NGAL levels in Group L patients recovered within normal limits (6.9 ± 4.33 - 4.50 ± 1.23 ng/ml) as compared to Group C (7.31 ± 2.03 - 6.10 ± 2.15 ng/ml) after 24 hours (fig.2).

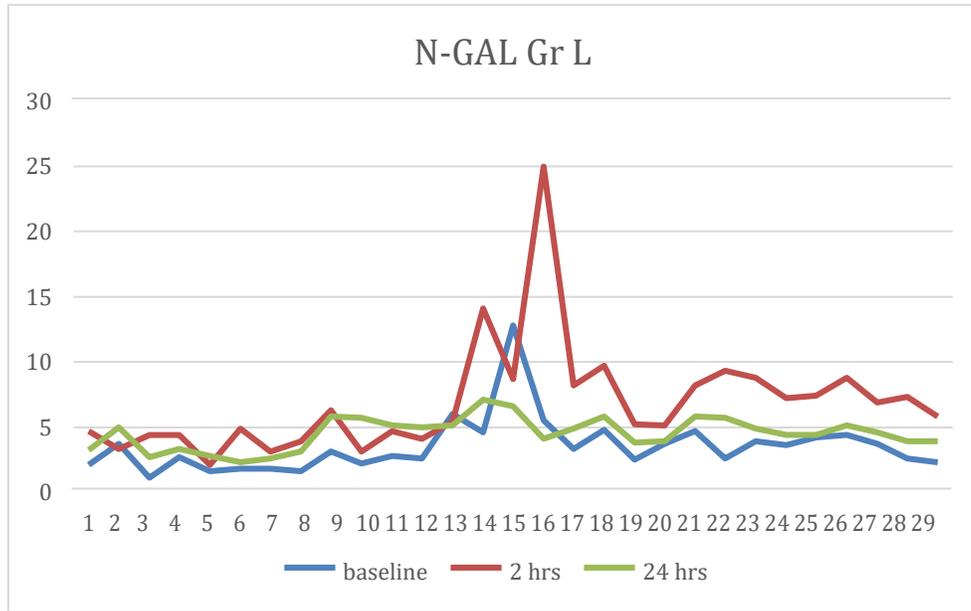


Figure 1

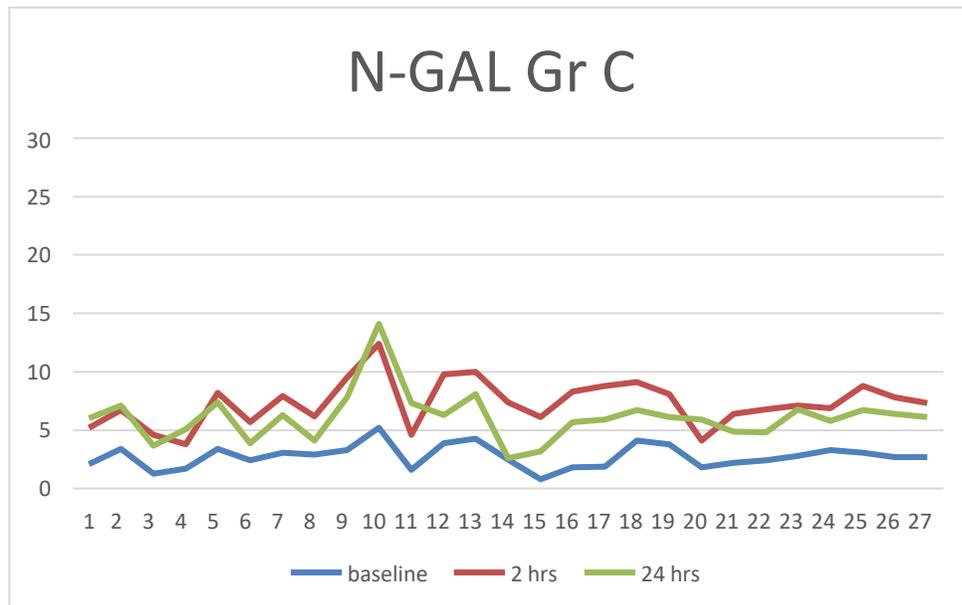


Figure 2

Serum creatinine when measured after 24 hours was found to have raised from 1.27 ± 0.38 to 1.65 ± 0.52 mg/dl in Group L (fig 3), while it had increased from 1.16 ± 0.25 mg/dl to 1.81 ± 0.36 mg/dl in Group C which was significant (fig 4).

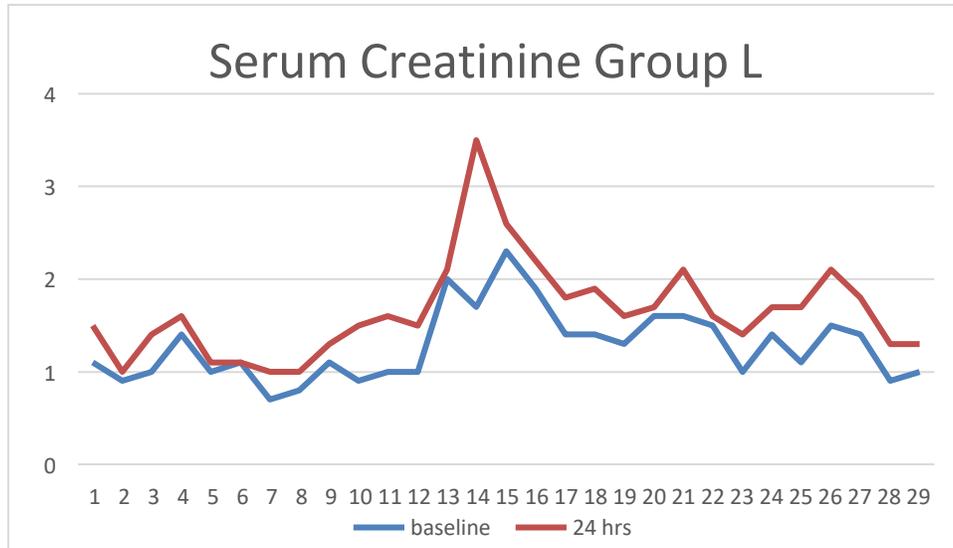


Figure 3

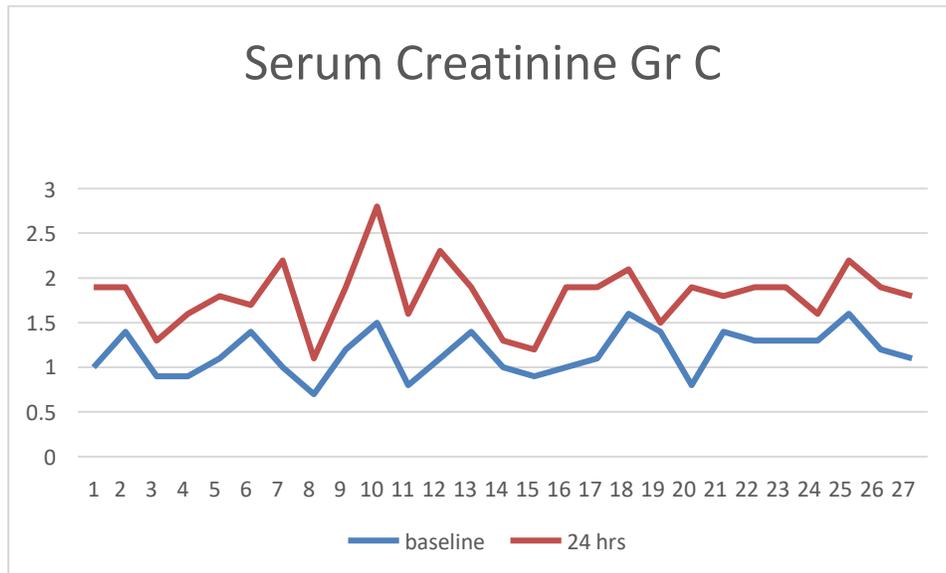


Figure 4

While the baseline cardiac index of the patients were comparable between the two groups (Group C 2.5 ± 0.41 vs Group L 2.7 ± 0.55), there was no discernible difference between the groups after 24 hours. The cardiac index of patients in Group C was 3.1 ± 0.92 while that of Group L was 3.6 ± 0.75 .

Mean duration of ICU stay was 5.2 ± 1.43 days in Group C and 4.1 ± 1.7 days in Group L. 3 mortalities were reported in Group C and 1 patient from Group L expired during the course of the study.

In Group C 14 patients (57.14% of the group) had acute kidney injury during the post-operative period while Group L had only 6 patients (18.75% of the group) affected by the same.

Discussion:

Serum creatinine levels have been historically used as a prognostic/diagnostic marker of AKI over the years. NGAL, which is a novel biomarker helps to detect renal cell injury as early as within two hours after the insult to renal tissue has occurred.⁷

The hemodynamic changes are not uncommon during cardiac surgery especially in off pump cases. It is because of manipulation of heart during various phases of coronary revascularization, the heart rate, systemic blood pressure and at times diastolic blood pressure changes occur. These fluctuations in hemodynamics cause ischemia reperfusion injury at all vascular systems either macro vascular or microvascular.²

Due to this there is release of oxygen free radicle substances which further accentuate this injury at various vascular system. However this is more hazardous in renal system. It is because all the biochemical lab results reflect the injury only after 24 to 48 hrs of renal injury. Initially urine output measurements may be normal to average in the patients who undergo off pump coronary artery bypass grafting surgery. However by the time the reduction in renal output is revealed it must have passed the many hours of renal cell injury which has not taken care of.⁸

Also there is high possibility of fluctuations in hemodynamics in postoperative period because of various surgery related reasons. So all this cause, severe impact on outcome of surgery and also patient outcome delaying the postoperative recovery of otherwise moderate risk patient.

After successful impact of levosimendan as an inotropic agent for patients with acute and chronic heart failure, several promising human studies on levosimendan usage in cardiac surgery have been published recently suggesting levosimendan can be beneficial in low-output states after cardiac surgery. In this era of Evidence Based Medicine any new therapy can only be adopted for universal clinical usage after it has been validated by rigorous scrutiny of current best available scientific evidence. In the hierarchy of clinical evidence, the randomized clinical trial (RCT) is generally considered the best approach to ascertain the value of a particular therapy.⁹

However, a logical and comprehensive approach to evaluating clinically relevant research incorporates many different types of evidence including RCTs, nonrandomized clinical trials, and experimental data and analyzes the information's content for its consistency, coherence and clarity [41]. The next section of this review evaluates the current best available evidence to validate the safety and efficacy of the perioperative use of levosimendan in cardiac surgical patients with high perioperative risk, compromised left ventricular function, or with difficulties in weaning from CPB.⁹

In our study, 80 percent of patients who received prophylactic Injection Levosimendan had smooth and faster recovery without any renal problems which required renal replacement therapy. On the contrary 8 to 10 percent of patients who did not receive prophylactic Levosimendan required either loop diuretics usage more or there was requirement of renal replacement therapy.

The generalized argument among the cardiac Surgeons and Cardiac Anaesthesiologists is about the use of Levosimendan in patient who are having moderate left ventricular function undergoing off pump Coronary artery bypass grafting. It is because of the possibility of hypotension in the perioperative period.

To our experience whenever we used Levosimendan as a prophylactic measure in off pump CABG surgery along with minimal dosage of infusion of Norepinephrine we never faced significant hemodynamic changes which neither required to stop the Levosimendan infusion nor to step up norepinephrine infusion doses, to maintain systemic vascular resistance. So the timing to start Levosimendan infusion and masterly monitoring of all vital parameters with their ongoing trends becomes a key factor to avoid levosimendan induced side effects. In addition to that Levosimendan improves systolic function without increasing myocardial oxygen demand unlike other ionodilators like Dobutamime or Milirinone. This has been shown by the study done by Ukkonen and colleagues employing positron emission tomography with acetate to measure myocardial oxygen consumption noninvasively and assess myocardial efficiency in 16 healthy men, clearly showed that myocardial oxygen consumption per heart beat was unchanged with levosimendan, as opposed to being increased with dobutamine.⁹

Lilleberg and colleagues performed the first ever randomized, double-blind study to evaluate the effects on systemic and coronary hemodynamics and myocardial substrate utilization of levosimendan after coronary artery bypass grafting (CABG). Twenty-three low-risk patients, with ejection fraction greater than 30% and isolated coronary artery disease, received placebo (n 8), 8 mcg/kg(n 8) or 24 mcg/kg (n 7) of levosimendan after elective CABG. Systemic and coronary sinus hemodynamics with thermodilution and myocardial substrate utilization were measured. The heart rate (HR) increased by 11 beats/minute after the higher dose (p 0.05). Cardiac output increased by 0.7 and 1.6l/minute (p 0.05 for both) after 8 and 24 mcg/kg of levosimendan, respectively. Systemic and pulmonary vascular resistance decreased after both doses significantly. Coronary sinus blood flow increased by 28 and 42 mL/minute (p 0.054 for the combined effect) after the lower and higher dose, respectively. Despite improved cardiac performance, levosimendan did not increase myocardial oxygen consumption or change myocardial substrate utilization.⁹

Nijhawan and colleagues confirmed and extended the findings of Lilleberg and colleagues. In their randomized, double-blind, placebo-controlled trial, 18 elective patients, with ejection fraction greater than 30%, were randomly assigned to receive levosimendan (18 or 36 mcg/kg loading dose and 0.2 or 0.3 mcg/kg/minute infusion, respectively) or placebo 15 minutes before and continued for 6 hours after CPB. Immediate and sustained increases in CO and reductions in SVR after CPB were obtained with loading doses followed by continuous infusions of levosimendan.⁹

Hence if we review literature there are very few studies which mention the prophylactic use of levosimendan infusion in off pump CABG surgery where the Cardiac Anaesthesiologist has the key role in managing hemodynamics and to get good outcome of procedure with faster recovery of the patient without any postoperative complications of renal system.

The off pump CABG offers the benefit of avoiding all the complications related to cardiopulmonary bypass. But it has to be noted that it is not only prolonged hypotension that causes renal cell injury but also the ischemia - reperfusion injury. This ischemia reperfusion injury may happen during the various manipulations and positioning the heart during coronary anastomosis especially posterior anastomosis like Obtuse marginal coronary vessel or posterior descending artery vessel bypass grafting.²

In our study, we studied the prophylactic use of levosimendan offers the renal protection and it is very well correlated by using early renal biomarkers like NGAL.

In the latest editorial by Dr. Deepak Tempe it is said that there is considerable enthusiasm among the Asian countries (Japan, India, and South Korea) to perform OPCAB, with 50%-to-75% of patients undergoing OPCAB (JCVA editorial 2022). It is a way forward to be performed in high risk patients requiring Coronary artery Bypass surgery.¹⁰

So levosimendan with minimal vasopressor support will definitely help perioperative outcome of patient as well as the procedure. The lusitropic effect and vasodilator effect of levosimendan is beneficial to reduce ischemia reperfusion injury at major as well as micro vasculature.

In our study we observed the beneficial effect of renal vasodilation in levosimendan study group than the control group. This has been estimated by NGAL Biomarker levels. It was statistically significant.

Conclusion:

Levosimendan offer renal protection during off pump coronary artery bypass grafting surgery. Use of plasma neutrophil gelatinase-associated lipocalin(n-gal) as an early marker of acute kidney injury is useful to prevent perioperative renal complications.

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